REMARKS

Applicants respectfully request reconsideration of the present application in view of the reasons that follow.

I. Status of the Claims

Claims 1, 4, 6-18, 22, 23, 25, 27, 30 and 31 are currently amended. Claims 2, 3 and 5 were previously canceled. Hence, upon entry of this paper, Claims 1, 4, 6-25 and 27-31 will remain pending. The Examiner states that Claims 1, 4, 6-10, 13-15, 23-25 and 31 are currently under examination and claims 11, 12, 16-22 and 27-30 are withdrawn.

The amendments to the specification are made to correct hyperlink embedded data and further define known reagents. No new matter has been added to the specification.

The cancellation of any claims does not constitute acquiescence in the propriety of any rejection set forth by the Examiner. Applicants reserve the right to pursue the subject matter of the canceled claims in subsequent divisional applications.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claims remain under examination in the application, is presented, with an appropriate defined status identifier.

II. The Restriction/Election Requirement

Applicants have reviewed the Examiner's reasons for maintaining the voluminous restriction requirement, under 35 U.S.C. §§ 121 and 372, and Applicants respectfully do not agree with the Examiner's position and reasons for maintaining the restriction requirement. Applicants wish to remind the Examiner that pursuant to MPEP § 1850, in PCT national phase cases (§371 cases), the Examiner is required to follow the determination of the International Bureau and cannot *sua sponte*, set forth his own groupings for purposes of examination. See, for example, *Caterpillar Tractor Co. v Commissioner of Patents*, 650 F.Supp. 218, 231 USPQ 590 (VA 1986). Applicants wish to reiterate that the International

Searching Authority did not make a determination that there was a lack of unity among the claims searched in the corresponding PCT application, PCT/EP2005/001573.

Further, the Examiner states that the alleged inventions listed in the restriction requirement do not relate to a single general inventive concept under PCT Rule 13.1, which according to the Examiner, under PCT Rule 13.2, lack the same or corresponding special technical features. In support of his position that the multiple alleged inventions do not have a special technical feature which link the inventions one to the other, the Examiner states that claim 1 lacks inventive step over WO 96/26964 A1 [Weiner *et al.*] because the Examiner interprets this document as allegedly disclosing a 91% identity to SEQ ID NO: 2 under stringent conditions.

Applicants respectfully disagree with the Examiner's *a priori* inventive step rejection of the claims before an Office Action has been issued, and Applicants also wish to point out that Claim 1 no longer contains the language in previous section (iii) related to hybridization results. Applicants reserve the right to traverse should the Examiner rely on Weiner *et al.* in rejecting the claims in an Office Action.

Applicants further submit that the Examiner's position is unfounded because Claim 1 and all of the dependent claims possess an inventive step and share the same technical feature; i.e., each has a first domain specifically binding to the human CD3 complex, wherein the first domain comprises SEQ ID NO: 10. Applicants submit that the claimed bispecific single chain antibody construct has inventive step over Weiner *et al.* Additionally, the examination of the nucleic acid sequence that encodes the claimed bispecific single chain antibody construct should be examined with the Claims of Group I because there is no burden on the Examiner in searching these inventions together since an electronic sequence search will identify both the amino acid and nucleic acid sequences. Applicants acknowledge the finality of this restriction requirement, but Applicants reserve the right to rejoinder. Applicants note that upon allowance of any linking claims, the restriction requirement as to the linked inventions shall be withdrawn and any claims depending from or otherwise requiring all of the limitations of the allowable linking claims will be rejoined and fully examined for patentability in accordance with 37 C.F.R. 1.104.

III. Priority

The Examiner has erroneously determined that Claims 1, 4, 6-10, 13-15, 23-25 and 31 do not properly benefit under 35 U.S.C. §§ 119 and/or 120 "since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure." Then, based on this erroneous determination, the Examiner considers the effective filing date of the claims to be the PCT filing date of PCT/EP05/001573, of which the present application is a national stage filing under 35 U.S.C. § 371; i.e., February 16, 2005.

Applicants respectfully point out that the Examiner has incorrectly determined the alleged lack of priority of the above-identified application. Applicants submit that the above-identified application is entitled to the priority date of its priority document, EP Application 04003445.6 filed on February 16, 2004. This priority claim was included in the Application Data Sheet submitted at the time of the national stage filing on August 8, 2006. A comparison of the disclosures of EP Application 04003445.6 and PCT/EP05/001573 will show that these documents are identical or almost identical in their disclosures. Applicants submit that the Examiner has no legitimate basis to deny priority of the pending claims back to February 16, 2004, the filing date of EP Application 04003445.6, because this priority document discloses the claimed invention. Applicants further submit that the Examiner's alleged position that the disclosure in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. §112 to properly claim priority is not sufficient to deny Applicants' priority claim back to February 14, 2004. Therefore, it is requested that this rejection be withdrawn.

IV. Specification

The Examiner has objected to alleged informalities in the specification based on the designation of the known reagent SEPHADEX® and embedded hyperlinks. Applicants have amended to the specification as requested by the Examiner, and it is requested that these objections be withdrawn in view of these amendments.

V. Claim Objections

The Examiner has made several claim objections to the language of Claim 23-25 and 1, 7, and 15 as well as the claims that depend from these claims. Applicants have amended the claims accordingly, and it is requested that these objections be withdrawn.

VI. Claim Rejections – U.S.C. § 112, Second and First Paragraphs

A. U.S.C. § 112, Second Paragraph

1. Claims 1, 4, 6-10, 13-15, 23-25 and 31

The above claims are rejected as indefinite in the recitation of "interacts with" or "antigen-interaction site" in the claims. The Examiner states that he does not know the metes and bounds of these phrases as compared to "specifically binds." Applicants submit that paragraphs [0022] – [0024] of the specification of the published application provide sufficient definition and discussion of the meaning of the phrases "interacts with" or "antigen-interaction site" to support the definiteness of these phrases in the claims. Although Applicants do not acquiesce to the propriety of this rejection, but in an effort to expedite prosecution, Applicants have deleted these phrases from the claims. Therefore, it is requested that this rejection be withdrawn.

2. Claims 1, 4, 6-10, 13-15, 23-25 and 31

The above claims are rejected as indefinite in the recitation of "or is encoded" in the claims. The Examiner alleges that it is unclear what is encoded by a nucleic acid sequence of SEQ ID NO: 9. Applicants have amended claim 1 to recite that the first domain's amino acid sequence of the antibody light chain is encoded by SEQ ID NO: 9. Therefore, it is believed that this rejection has been obviated.

3. Claims 1, 4, 6-10, 13-15, 23-25 and 31

The above claims are rejected as indefinite in the recitation in claim 1 of "wherein one of said at least two domains specifically binds to/interacts with the human CD3 complex, wherein said domain...." Applicants have amended claim 1 to clarify that the domain that

specifically binds the human CD3 complex is the "first domain" of the at least two domains. Applicants thank the Examiner for his claim language suggestions, but Applicants believe that because the phrase "second domain" is recited in the claim, inserting the phrase "first domain" should clarify this issue and overcome the rejection.

4. Claims 13 and 14

The above claims are rejected as indefinite in the recitations of "an amino acid sequence corresponding to" and "encoded by a nucleic acid sequence corresponding to" because the Examiner alleges that he cannot determine to what extent an amino acid sequence of a nucleic acid sequence must correspond to the recited sequences. Applicants have deleted the "corresponding to" language from these claims to provide clarity that the "amino acid sequence" or "nucleic acid sequence" are those SEQ ID NOs. recited in these claims. In view of these amendments, it is requested that this rejection be withdrawn.

5. Claim 25

The above claim is rejected as indefinite in the recitation of a composition that further comprises methods for detection. Although Applicants do not necessarily agree with the Examiner's rationale for rejecting this claim, Applications have amended claim 25 to delete the language, "further comprising means and methods." In view of this amendment, Applicants request that this rejection be withdrawn.

B. U.S.C. § 112, First Paragraph

1. Claims 1, 4, 6-10, 13-15, 23-25 and 31

The above claims are rejected as failing to comply with the written description requirement based on the Examiner's interpretation of the claim language. Specifically, the Examiner alleges that the first and second domains of the binding molecule are not sufficiently described and that the term "interaction" or "interacts" is not described for binding molecules other than bispecific antibodies. Additionally, the Examiner states that the claims encompass a structurally and functionally diverse genus of domains that only need to comprise amino acid sequence, SEQ ID NO: 10 or an amino acid encoded by SEQ ID NO: 9.

Although not acquiescing to the correctness of the Examiner's rejection, Applicants have amended the claims to recite that the binding molecules is "a bispecific single chain antibody construct," which language is supported in the specification, such as in paragraph [0049] of the published application. To those skilled in the art, the phrase "a bispecific single chain antibody construct" is interpreted as an antibody construct which contains two single chain Fvs, each Fv containing a VH and a VL portion of an antibody. Additionally, Applicants have deleted the word "derived" in Claim 1. Further, Claim 1 is limited to bispecific single chain antibody constructs that contain SEQ ID NO: 10, which is identified as a humanized CD3 VL sequence in the Sequence Listing.

With regard to the Examiner's comments on the Claim 8 language, Applicants submit that paragraph [0047] sufficiently describes "a tumor specific molecule(s)," and Applicants submit that one skilled in the art would be able to envision, recognize and predict whether any given antigen was a tumor specific antigen or not.

Therefore, in view of these arguments and amendments to the pending claims, Applicants submit that this rejection should be withdrawn.

2. Claims 1, 4, 6-10, 13-15, 23-25 and 31

The above claims are rejected as failing to be reasonable enabled for making and using the full scope of the claimed bispecific binding molecules that only consist of a light chain or heavy chain or a fragment of a light or heavy chain. The Examiner recites the Wands factors as supporting that the present specification does not provide guidance, direction and exemplification to enable the skilled person to make and/or use the claimed invention without undue and/or unreasonable experimentation. In this rejection the Examiner does state which subject matter is enabled by the specification on pages 19-21.

As previously argued, the pending claims have been amended to more clearly define the invention as comprising a bispecific single chain antibody construct that comprises SEQ ID NO; 10 [the humanized CD3 VL chain] or that is encoded by the nucleic acid sequence, SEQ ID NO: 9, and this portion of the antibody construct binds to the human CD3 complex. Additionally, the claims recite that the bispecific single chain antibody construct contains a

second antigen binding domain and, optionally, at least one effector domain. Therefore, the claimed bispecific single chain antibody construct by definition contains complete VL and VH regions in each domain of the construct.

Further, the Examples in the application provide guidance on constructing, purifying and testing the claimed bispecific single chain antibody constructs. Therefore, in view of these arguments and amendments to the pending claims, Applicants submit that this rejection should be withdrawn.

VII. Claim Rejections – U.S.C. § 102

A. Claims 1, 7, 8, 13-15, 23, 24 and 31

The above claims are rejected as allegedly anticipated by WO 98/47531 A2, (Smith *et al.*, 1998) (hereinafter referred to as "Smith"). The Examiner alleges that Smith discloses "...bispecific anti-CD3-Fos x anti-CD4-Jun binding molecules where the antigen binding domain that binds the human CD3 complex is from an OKT3 antibody which comprises two consecutive amino acids of an antibody of an antibody derived light chain having the amino acid sequence of SEQ ID NO: 10 a light chain and CD4 is a cell surface molecule."

Applicants respectfully disagree with the Examiner's position that Smith discloses the claimed bispecific single chain antibody constructs. A comparison of SEQ ID NO: 6 from Smith with SEQ ID NO: 10 of the present invention shows that the sequences are not the same, and, therefore, Smith does not anticipate the rejected claims.

Applicants request a clarification from the Examiner regarding his interpretation of Applicants' Claim 1 with regard to the domain that binds to the human CD3 complex. It is unclear why the Examiner would state in this rejection and other rejections over prior art that the "domain that specifically binds to the human CD3 complex comprises **an amino acid sequence, which is broadly, but reasonably interpreted as at least two consecutive amino acids of an antibody derived light chain having the amino acid sequence of SEQ ID NO: 10, ..."** First, Applicants submit that the previous claim language of Claim 1 could not have been interpreted so broadly as to read on only two consecutive amino acids of a prior art

sequence; and surely the amended set of claims cannot be interpreted so broadly. Applicants submit that Claim 1, as herein amended, is directed to a bispecific single chain antibody construct that contains at least two domains, and that the first domain that binds to the human CD3 complex must contain at least SEQ ID NO: 10, which is a humanized CD3 VL.

Therefore, in view of these arguments and amendments to the pending claims, Applicants submit that this rejection should be withdrawn.

B. Claims 1, 7-10, 13, 14, 23, 24 and 31

The above claims are rejected as allegedly anticipated by Mack *et al.*, *J. Imm.*, 158: 3965-3970, 1997) (hereinafter referred to as "Mack"). The Examiner alleges that Smith discloses "...bispecific anti-CD3-Fos x anti-CD4-Jun binding molecules where the antigen binding domain that binds the human CD3 complex is from an OKT3 antibody which comprises two consecutive amino acids of an antibody of an antibody derived light chain having the amino acid sequence of SEQ ID NO: 10 a light chain and CD4 is a cell surface molecule."

As with the rejection based on lack of novelty above for the Smith reference, the Examiner has broadly interpreted the claims as reading on two consecutive amino acids inherently present in Mack. Even though the Office lacks research facilities, Applicants submit that the Examiner simply has no basis to support his position that Mack anticipates the rejected claims. Mack does not provide any information that one could ascertain that the sequences of Mack's CD3 portion of the bispecific single chain antibody is the same as the claimed bispecific antibody constructs. Specifically, Mack does not provide any antibody sequences. Further, the Examiner states that Mack teach that antigen-binding domains may be humanized. [See the statements made by the Examiner in the obviousness rejection below where the Examiner combines Mack with Queen.]

Therefore, in view of these arguments and amendments to the pending claims, Applicants submit that this rejection should be withdrawn.

C. Claims 1, 4, 7-10, 13- 15, 23, 24 and 31

The above claims are rejected as allegedly anticipated by Kufer *et al.*, [US 20070081993 A1, effective filing date May 26, 2004) (hereinafter referred to as "Kufer"). The Examiner alleges that Kufer discloses a bispecific single chain anti-CD3 x anti-EpCAM binding molecule. However, Applicants submit that Kufer is not prior art under 35 U.S.C. § 102(e) because, as argued previously, the present application is entitled to its foreign priority date of February 16, 2004 based on a EP Application 04003445.6, submitted during the PCT phase of the present application. Also, see the IFW of the present application for a certified copy of the European priority document.

In support of Applicants' position, the Examiner is directed to the MPEP 2136.03, which recites:

> 35 U.S.C. § 102(e) is explicitly limited to certain references "filed in the United States before the invention thereof by the applicant" (emphasis added). Foreign applications' filing dates that are claimed (via 35 U.S.C. 119(a) - (d), (f) or 365(a)) in applications, which have been published as U.S. or WIPO application publications or patented in the U.S., may not be used as 35 U.S.C. 102(e) dates for prior art purposes. This includes international filing dates claimed as foreign priority dates under 35 U.S.C. 365(a).Therefore, the foreign priority date of the reference under 35 U.S.C. 119(a)-(d) (f), and 365(a) cannot be used to antedate the application filing date. In contrast, applicant may be able to overcome the 35 U.S.C. 102(e) rejection by proving he or she is entitled to his or her own 35 U.S.C. 119 priority date which is earlier than the reference's U.S. filing date. *In re Hilmer*, 359 F.2d 859, 149 USPQ 480 (CCPA 1966) (*Hilmer I*).

Therefore, in view of these arguments that Applicants' priority date is before the effective filing date of Kufer, Applicants submit that this rejection should be withdrawn as not being proper under 35 U.S.C. § 102(e).

VIII. Claim Rejections – U.S.C. § 103

Claims 1 and 15

The above claims are rejected as allegedly obvious over Mack *et al.*, *J. Imm.*, 158: 3965-3970, 1997) (hereinafter referred to as "Mack") in View of Queen *et al.*, [US 5,530,101] (hereinafter referred to as "Queen"). The Examiner applies Mack as applied in the lack of

novelty rejection above except that the Examiner in this rejection admits that "Mack does not expressly teach humanizing the antigen-binding domains, and utilizes Queen to teach this feature. The Examiner concludes that one of ordinary skill would be motivated to humanize the antigen-binding domains of Mack in view of Queen.

Applicants respectfully disagree with the Examiner's stated teachings of Mack and the obviousness of humanizing Mack's domains to arrive at the invention in Claims 1 and 15. First, Mack does not disclose an anti-CD3 portion of its single chain antibody that contains SEQ ID NO: 10 of the present invention even if it was humanized. Further, there is no predictability that a humanized bispecific antibody of Mack's would function by properly binding to CD3 antigen on the surface the T-cells. Example 4.2 in the present specification discloses better binding of the claimed bispecific single chain antibody constructs than with humanized OKT3.

For all of these reasons, this rejection should be withdrawn.

IX. Claim Rejections – Obviousness-type Double Patenting

A. Claims 1, 4, 7-10, 13-15, 23, 24 and 31

These claims are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12, 25 and 26 of USSN 10/554,851 that corresponds to claims 1-3 of US 7,919,089. The Examiner considers that the claims of the '089 Patent are drawn to single chain bispecific binding molecules that bind human CD3 and EpCAM comprising SEQ ID NO: 44 which shares two consecutive amino acids with the instantly recited SEQ ID NO: 10 and compositions or kits comprising said bispecific binding molecules. The Examiner has impermissibly used the specification as prior art to teach that antigen-binding domains may be humanized. Although the Examiner states that he is using the specification as a "dictionary," Applicants submit that he is using this teaching from the specification as prior art.

It is, therefore, requested that this rejection be withdrawn because the amended claims are clearly not obvious over claims 1-3 of the '089 patent. But, alternatively, because there

are no allowed claims in the present application, it is requested that this rejection be held in abeyance until allowable subject matter is indicated by the Examiner.

B. Claims 1, 4, 7-10, 13-15, 23, 24 and 31

These claims are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 9, 13, 15-20, 33-35 and 41 of copending USSN 10/572,740. The Examiner considers that the claims of the '740 application are drawn to single chain bispecific binding molecules that bind human CD3 and EpCAM, where the domain that binds CD3 comprises SEQ ID NOs: 98, 100 and 104 which shares two consecutive amino acids with the instantly recited SEQ ID NO: 10 and compositions or kits comprising said bispecific binding molecules.

It is, therefore, requested that this rejection be withdrawn because the amended claims are clearly not obvious over claims 1-7 9, 13, 15-20, 33-35 and 41 of copending USSN 10/572,740. But, alternatively, because there are no allowed claims in the present application, it is requested that this rejection be held in abeyance until allowable subject matter is indicated by the Examiner.

C. Claims 1, 4, 7-9, 13-15, 23, 24 and 31

These claims are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 8 of US 7,635,472. The Examiner considers that the claims of the '472 Patent are drawn to single chain bispecific binding molecules that bind human CD3 and a cell surface antigen, wherein the domain that binds CD3 comprises the amino acid sequences of SEQ ID NOs: 55, 56 and 57 which shares two consecutive amino acids with the instantly recited SEQ ID NO: 10 and compositions or kits comprising said bispecific binding molecules. The Examiner has impermissibly used the specification as prior art to teach that antigen-binding domains may be humanized. Although the Examiner states that he is using the specification as a "dictionary," Applicants submit that he is using this teaching from the specification as prior art.

It is, therefore, requested that this rejection be withdrawn because the amended claims are clearly not obvious over claims 1-6 and 8 of 472 patent. But, alternatively, because there are no allowed claims in the present application, it is requested that this rejection be held in abeyance until allowable subject matter is indicated by the Examiner.

CONCLUSIONS

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date July 1, 2011

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